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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CRUZ, KATHRIEN ANN	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,327	MEYTHALER ET AL.	
	Examiner	Art Unit	
	KATHRIEN CRUZ	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,29,34-36 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,29,34-36 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 7, 29, 34-36 and 40 are pending.

Applicants response dated November 13, 2008 has been received and entered into the application.

Priority

This application has claimed priority to application PCT/US00/21893 filed 08/10/2000 that claim benefits to provisional application 60/148, 068 filed 08/10/1999.

Action Summary

Applicant's arguments, filed November 13, 2008, with respect to the rejection(s) of claim(s) 1, 7, 29, 34-36, and 40 under 35 U.S.C. §103(a) have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, 29 and 36 are rejected under 35 U.S.C.112, first paragraph, because the specification, while being enabling for making and using salts of the claimed compounds, does not reasonable provide enablement for making and using solvates or hydrates of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of tat art, h) and the breadth of the claims", I re Rainer, 146 USPQ 218 (1965); *In re Colianni,* 195 USPQ 150, *ex parte formal,* 230 USPQ 546. a) Finding a solvates or hydrates is an empirical exercise. Predicting if a certain ester of claimed alcohol, for example, is in fact a solvates or hydrates, that produces the active compound metabolically, in man, at a therapeutic concentration and a t a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo* , this is still an experimental science. For a compound to be a solvates or hydrates, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three

criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the solvates or hydrates is found in the specification on page 21. c) There is no working example of a solvates or hydrates of a compound the formula II. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrugs art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to fine a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicated the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the solvates or hydrates concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence is particularly relevant. f) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F2d 833, 839, 166 USPQ 18, 24 (CCPQ 1970). g) The breadth of the claims includes all of the hundreds of thousand of compounds of formula of claim 1 as well as the presently unknown list of potential solvates or hydrates embraced by claim 1.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make

and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 7, 29, 34-36 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Breitner et al (U.S. Patent 5,643,960) in view of Bustamante et al (Effects of Intrathecal or Intracerebroventricular Administration of Nonsteroidal Anti-inflammatory Drugs on a C-Fiber Reflex in Rats, Journal of Pharmacology and Experimental Therapeutics, Vol. 281. No.3, 1997) and Grilli (WO 98/20864), all of the references are of record.

Applicant claims a method for treating a subject having inflammation associated with neurotrauma, said method comprising intrathecally administering by intrathecal catheter to the subject a therapeutically effective amount of choline magnesium trisalicylate or prodrug thereof non-inhibitory of platelets so as to reduce the inflammation associated with the neurotrauma.

Breitner teaches a method of delaying the onset of **Alzheimer's disease or related neurodegenerative disorders** associated with excitotoxic neuronal cell death (for example, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, Parkinson's disease, and Pick's disease). The method comprises administering to an individual at risk of developing the disease (or disorder) an amount of a nonsteroidal anti-inflammatory agent (column 3, lines 7-14). Breitner teaches that the Nonsteroidal anti-inflammatory agents suitable for use in the present invention include the arylcarboxylic acids (**salicylic acid, acetylsalicylic acid**, diflunisal, **choline magnesium trisalicylate**, salicylate (column 3, lines 39). Breitner teaches that all of these NSAIDs are potent inhibitors of cyclooxygenase (COX) (column 3, line 51-52).

Breitner does not expressly teach administering NSAIDs intrathecally or intraventricularly, and further administering a deacetylated aspirin (an active metabolite of aspirin) for the treating of Alzheimer's disease associated with neuronal cell death.

Bustamante teaches a method of administering intrathecally aspirin with a dosage range from 10μg to 500μg and other NSAIDs with a dosage range from 100μg to 500μg (table 1) (page 1383). Bustamante teaches a method of administering intracerebroventricularlly aspirin with a dosage of 500 μg and NSAIDs with a dosage of 250 or 500μg (table 1) (page 1383).

Grilli et al. teaches the treatment of Alzheimer's disease through the use of NSAIDs (Abstract). Sodium salicylate and salicylamide are specifically taught as NSAIDs useful in the invention disclosed therein (page 3, lines 1-10). Neuronal damages (i.e. neurotrauma or neuronal injury) related to Alzheimer's disease, Parkinson's disease, spinal traumas and cranial traumas as well as other neurodegenerative processes are specifically taught as treatable by the NSAIDs disclosed therein (page 6, lines 9-20). Grilli et al. teach, on page 5, lines 1-10, that non-steroidal anti-inflammatory drugs can be used in the prevention and/or treatment of glutamate receptor-mediated neuronal damages, independently of any anti-inflammatory properties. Grilli et al teaches that a preferred embodiment is the use of **ASA or of it's metabolite (e.g., deacetylated aspirin)**, for the treatment of glutamate receptor-mediated neuronal damages (page 3, lines 11-14). Further the NSAIDs show a protective activity against glutamate-induced neurotoxicity.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to modify the teachings of Breitner to include the administration of

NSAIDs intrathecally or intraventricularly. One would be motivated to make such a modification because anti-inflammatory agents and aspirin may be administered **intrathecally and intracerebroventricularlly** as taught by Bustamante. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; **mode of administration**, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and **modes of administration**. Furthermore, no unobviousness is seen in the ratio claimed because once the usefulness of a compound is known to treat a condition, it is within the skill of the artisan to determine the optimum ratio.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to incorporate deacetylated aspirin in the method of Breitner to treat Alzheimer's disease associated with neuronal injuries because it is known in the art that non-steroidal anti-inflammatory drugs can be used in the treatment of glutamate receptor-mediated neuronal damages, independently of any anti-inflammatory properties as taught by Grilli. One of ordinary skill in the art would have been motivated to make such a modification because employing any known NSAID, including **ASA or of it's metabolite (i.e., deacetylated aspirin)**, for the treatment of neuronal damages as taught in Breitner would be reasonably expected to be effective. At least additive effect is expected

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments with respect to claims 1, 7, 29, 34-36 and 40 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Claims 1, 7, 29, 34-36 and 40 are rejected.

No claims allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Mon - Thurs 7:00am - 5:00pm with every Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN CRUZ/
Examiner, Art Unit 1617

/San-ming Hui/
Primary Examiner, Art Unit 1617